Note

Rearrangement of dehydro-L-ascorbic acid 2-phenylhydrazone 3-semicarbazone to a pyrazole derivative

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In continuation of our work on the synthesis of nitrogen heterocycles from dehydro-L-ascorbic acid mono- and bis-hydrazones $^{1-5}$, we describe herein the rearrangement of dehydro-L-ascorbic acid 2-phenylhydrazone 3-semicarbazone⁶ to a pyrazole derivative. Some of the 4.5-pyrazolinediones have shown great biological activity 7^{-10} , and this attracted our attention to preparation of more of these compounds. Thus, treatment of dehydro-L-ascorbic acid monophenylhydrazone (L-threo-2,3-hexodiulosono-1,4-lactone 2-phenylhydrazone) 11,12 (1) with one equivalent of semicarbazide hydrochloride afforded the 2-phenylhydrazone 3-semicarbazone (2). Boiling of compound 2 with liquid ammonia afforded 3-(L-threo-glycerol-1-yl)-4.5-(1H)-pyrazoledione 4-(phenylhydrazone) (4) on the basis of elemental analysis, and infrared and mass-spectral data. Its infrared spectrum showed carbonyl absorption at 1660 cm^{-1} (OCN), in addition to hydroxyl absorption at 3450 cm^{-1} , and its elemental analysis agreed with the molecular formula $C_{12}H_{14}N_4O_4$. The mass spectrum of 4 showed a molecular-ion peak (also the base peak) at m/z 278, corresponding to structure 4. This was followed by a series of ions arising from elimination processes involving the sugar moiety and the heterocyclic ring.

Acetylation of compound 4 with boiling acetic anhydride afforded 1-acetyl-3-(tri-O-acetyl-L-threo-glycerol-1-yl)-4,5-pyrazolinedione 4-phenylhydrazone (6). The infrared spectrum of 6 showed carbonyl absorption at 1660 cm⁻¹ in addition to an ester band at 1740 cm⁻¹. The n.m.r. spectrum of 6 showed three acetyl-group signals, at δ 1.87, 1.93, and 2.00, in addition to an N-acetyl group signal at δ 2.35. On the other hand, treatment of compound 5 with benzoyl chloride and pyridine, afforded a perbenzoate (7), designated 3-benzoyloxy-5-(tri-O-benzoyl-L-threo-glycerol-1-yl)pyrazolin-4-one 4-(2-benzoyl-2-phenylhydrazone). Its infrared spectrum showed an ester band at 1740 cm⁻¹, and the amide band (at 1660 cm⁻¹) of its precursor was

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absent. The pyrazole derivative exists as the keto (4) and enol (5) forms, the enol form 5 being favored in the presence of a base such as pyridine.

Periodate oxidation of one mol of compound 4 resulted in the consumption of two mol of the oxidant with the formation of 3-formyl-4,5(1H)-pyrazolinedione 4-phenylhydrazone (8). The infrared spectrum of 8 showed a broad band at 1680 cm⁻⁺ due to the aldehyde and the amide groups. Reduction of compound 8 with sodium borohydride afforded 3-(hydroxymethyl)-4.5(1H)-pyrazolinedione 4-phenylhydrazone (9). Acetylation of 9 with boiling acetic anhydride gave 3-(acetoxymethyl)-1-acetyl-4,5-pyrazolinedione 4-phenylhydrazone (10). The infrared spectrum of 10 showed amide absorption at 1660 cm⁻¹, in addition to an ester band at 1740 cm⁻¹. On the other hand, acetylation of compound 9 with acetic anhydride and pyridine afforded 5-(acetoxymethyl)-3-acetoxypyrazol-4-one 4-(2-acetyl-2-phenylhydrazone) (11). Its infrared spectrum showed an ester band at 1740 cm⁻¹, and there was no amide absorption. The n.m.r. spectrum of 11 showed three singlets, each of three-proton intensity; the first, at δ 2.08, was due to the 5-(acetoxymethyl) group: the second, at δ 2.38, was due to the acetyl group on O-3, deshielded by the heterocyclic ring; and the third, at δ 2.68, was attributed to the acetyl group on the hydrazone residue. The spectrum also showed a singlet, of two-proton intensity, at δ 5.8 (CH₂ group), and the phenyl group appeared as a multiplet at δ 7.30–7.82. Similarly, benzoylation of 9 with benzoyl chloride and pyridine gave the tribenzoyl derivative (12). The mass spectrum of compound 12 showed a molecular-ion peak at mz 530, followed by a series of peaks due to the elimination of the benzoyl groups.

On condensation of compound 8 with hydroxylamine, 3-formyl-4.5(1*H*)pyrazolinedione 4-phenylhydrazone 3-oxime (13) was obtained. Similarly, when aldehyde 8 was treated with phenyl-, (*p*-bromophenyl)-, (*p*-chlorophenyl)-, and (*p*-nitrophenyl)-hydrazine, it yielded the corresponding hydrazones 14-17 (see Table

TABLE I

SOME PROPERTIES OF COMPOUNDS 13-19

Com- pound	R	M.p. (degrees)	Molecular formula	Analysis			v (cm ⁻¹)		
					C	Η	N	ОН	OCN
13	ОН	242–243	$C_{10}H_9N_5O_2$	Calc.	51.95	3.92	30.27	3320	1660
				Found	51.74	3.60	29.84		
14	NHC ₆ H ₅	237–238	$C_{16}H_{14}N_6O\cdot H_2O$	Calc.	59.26	4.97			1660
				Found	59.16	4.59			
15	NHC ₆ H ₄ Br-p	211-212	C ₁₆ H ₁₃ BrN ₆ O	Calc.	49.89	3.40	21.80		1660
				Found	50.24	3.62	21,60		
16	NHC ₆ H ₄ Cl-p	262–263	C ₁₆ H ₁₃ ClN ₆ O	Calc.	56.40	3.84	24.65		1660
				Found	56.74	3.63	24.82		
17	NHC6H4NO2-p	274–275	$C_{16}H_{13}N_7O_3 \cdot 0.5 H_2O$	Calc.	53.34	3.91	27.20		1660
				Found	53.24	3.96	27.60		
18	NHCONH ₂	239–240	$C_{11}H_{11}N_7O_2$	Calc.	48.35	4.05	35.85		1660
				Found	48.06	4.21	35.62		
19	NHCSNH ₂	238–239	C11H11N7OS	Calc.			33.91	1660	
				Found			33.46		



I). Also, it was condensed with semicarbazide, and thiosemicarbazide, to give compounds **18** and **19**, respectively (see Table I).

Reaction of 8 with o-phenylenediamine afforded the pyrazole imidazole (20); its i.r. spectrum showed an NH band at 3160 cm⁻¹, and the amide band at 1660 cm⁻¹.

EXPERIMENTAL

General methods. -- Melting points were determined with a Tottoli (Büchi) apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 580 B spectrometer, and n.m.r. spectra (for solutions in chloroform-*d*, with tetramethylsilane as the standard) with Perkin-Elmer R 12 B and Cameca 250 spectrometers. Chemical shifts are given on the δ scale. Mass spectra were recorded with an LKB 2091 spectrometer; intensities are given in parentheses, as percentages of the base peak. Microanalyses were performed in the Service Central d'Analyse du CNRS, France.

L-threo-2,3-Hexodiulosono-1,4-lactone 2-phenylhydrazone 3-semicarbazone (2). — A solution of L-threo-2,3-hexodiulosono-1,4 lactone¹¹⁻¹³ (1, 1 g) in ethanol (50 mL) was treated with semicarbazide hydrochloride (1 g), sodium acetate (1 g), and a few drops of acetic acid, and the mixture was boiled under reflux for 3 h, cooled, and concentrated. The solid that separated out was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.8 g). Compound 2 crystal-lized from ethanol in orange needles, m.p. 210-211 (lit.⁶ m.p. 208-211).

3-(L-threo-Glycerol-1-yl)-4,5(1H)-pyrazolinedione 4-phenylhydrazone (4). A solution of compound 2 (1 g) in liquid ammonia (40 mL) was heated under reflux for 3 h, concentrated to 10 mL, and left to cool. The solid that separated was filtered off, and dried (yield 0.5 g). Compound 4 was recrystallized from ethanol: yellow needles, m.p. 140–141'; v_{max}^{kBr} 3450 (OH) and 1660 cm⁻¹ (OC N), *m* z 279 (60), 278 (100), 261 (16), 260 (20), 247 (40), 229 (76), 217 (38), 201 (70), 200 (18), 189 (49), 188 (20), 173 (24), 172 (49), 160 (40), 144 (28), 143 (36), 142 (22), 139 (44), 126 (17), 119 (16), 106 (26), 105 (66), 104 (66), 98 (46), 93 (66), 92 (40), 91 (10), 78 (10), 77 (80), 65 (60), and 61 (26).

Anal. Calc. for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.12 Found: C, 51.61; H, 4.84; N, 20.49.

1-Acetyl-3-(tri-O-acetyl-1.-threo-*glycerol-1-yl)-4,5-pyrazolinedione* 4-phenylhydrazone (6). — A suspension of compound 4 in acetic anhydride (10 mL) was boiled under reflux for 1 h. The mixture was poured onto crushed ice, and evaporated under diminished pressure to a thin syrup. Pure sample was obtained by preparative, thin-layer chromatography on silica gel using 3:1 (v/v) methanol-bexane as eluant: v_{max}^{Nujol} 1740 (ester) and 1660 cm⁻¹ (OCN); ¹H-n.m.r. data (CDCl₃) δ 6.15 (d, 1 H, H-1), 5.7 (q, 1 H, H-2), 4.26 (m, 2 H, H-3), 1.87, 1.93, and 2 00 (9 H, 3 OCOCH₃), 2.35 (s, 3 H, NCOCH₃), and 7.22–7.82 (m, 5 H, phenyl).

Anal. Cale. for $C_{20}H_{22}N_4O_8$: C, 53.81: H, 4.96: N, 12.54. Found: C, 53.62; H, 4.71; N, 12.84.

3-Benzoyloxy-5-(tri-O-benzoyl-L-threo-glycerol-1-yl)pyrazolin-4-one 4-(2-benzoyl-2-phenylhydrazone) (7). — A solution of compound 5 (0.1 g) in dry pyridine (10 mL) was treated with benzoyl chloride (0.2 mL) and kept for 4 days at room temperature. The mixture was poured onto crushed ice, and the solid that separated was filtered off, successively washed with water and ethanol, and dried (yield 0.1 g). Recrystallization from methanol gave compound 7 as yellow needles, m.p. 161–162°; v_{max}^{KBr} 1740 cm⁻¹ (ester).

Anal. Calc. for $C_{40}H_{30}N_4O_8 \cdot 0.5 H_2O$: C, 68.29; H, 4.44; N, 7.96. Found: C, 68.13; H, 4.21; N, 8.40.

3-Formyl-4,5(1H)-pyrazolinedione 4-phenylhydrazone (8). — A suspension of compound 4 (1 g) in water (30 mL) was treated with a solution of sodium metaperiodate (2 g) in water (20 mL), and the mixture was kept overnight at room temperature with shaking. The resulting solid was filtered off, successively washed with water and ethanol, and dried (yield 0.6 g; 74%). Recrystallization from ethanol gave compound 8 as orange needles; m.p. 188–189°; y_{max}^{KBr} 1680 cm⁻¹ (COH and OCN).

Anal. Calc. for $C_{10}H_8N_4O_2 \cdot 0.5 H_2O$: C, 53.33; H, 4.03; N, 24.86. Found: C, 53.55; H, 4.00; N, 24.72.

3-(Hydroxymethyl)-4,5(1H)-pyrazolinedione 4-phenylhydrazone (9). — A solution of compound 8 (0.2 g) in methanol (20 mL) was treated with a solution of sodium borohydride (0.3 g) in water (10 mL), added in small portions with occasional shaking. The solution was acidified with acetic acid, and the solid that separated was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.1 g). It was recrystallized from ethanol, to give yellow needles, m.p. 178–179°; ν_{max}^{KBr} 3450 (OH) and 1660 cm⁻¹ (OCN).

Anal. Calc. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.66. Found: C, 55.03; H, 4.56; N, 25.84.

3-Acetoxymethyl-1-acetyl-4,5-pyrazolinedione 4-phenylhydrazone (10). — A suspension of compound 9 (0.1 g) in acetic anhydride (5 mL) was boiled under reflux for 1 h. The mixture was poured onto crushed ice, and the product that separated was filtered off, successively washed with water and ethanol, and dried (yield 60 mg). Recrystallization from ethanol gave compound 10 as yellowish-orange needles, m.p. $153-154^{\circ}$; v_{max}^{KBr} 1740 (OAc) and 1660 cm⁻¹ (OCN); ¹H-n.m.r. data (CDCl₃): δ 2.08 (s, 3 H, OAc), 2.52 (s, 3 H, NAc), 5.16 (s, 2 H, methylene), and 7.3-7.65 (m, 5 H, phenyl).

Anal. Calc. for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.66; N, 18.52. Found: C, 55.59; H, 4.68; N, 18.32.

5-(Acetoxymethyl)-3-acetoxypyrazol-4-one 4-(2-acetyl-2-phenylhydrazone) (11). — A solution of compound 9 (0.1 g) in dry pyridine (10 mL) was treated with acetic anhydride (10 mL), and the mixture was kept for 4 days at room temperature, and poured onto crushed ice. The solid that separated was filtered off, successively washed with water and ethanol, and dried (yield 50 mg). Compound 11 was recrystallized from ethanol-benzene; yellow needles, m.p. $125-126^{\circ}$; $v_{\text{max}}^{\text{KBr}}$ 1740 cm⁻¹ (ester); m/z 219 (12), 218 (100), 201 (18), 200 (44), 189 (20), 172 (38), 172 (66),

160 (10), 159 (10). 143 (22). 142 (20), 141 (60), 131 (18), 126 (42), 116 (36), 115 (36), 111 (10), 105 (36), 104 (24), 98 (24), 92 (46), 91 (10), 83 (30), 78 (26), 77 (80), and 55 (42).

.4nal. Calc. for $C_{16}H_{16}N_4O_5$: C. 55.81; H. 4.68; N. 16.26. Found: C. 55.40; H. 4.32; N. 16.64.

5-(*Benzovloxymethyl*)-3-benzyloxypyrazol-4-one 4-(2-benzoyl-2-phenvlhydrazone) (12). -- A solution of 9 (0.1 g) in dry pyridine (10 mL) was treated with benzoyl chloride (0.1 g), and the mixture was kept for 4 days at room temperature, and poured onto crushed ice. The solid was filtered off, washed successively with water and ethanol, and dried (yield 40 mg). Compound 12 was recrystallized from ethanol: yellow needles. m.p. 157-158 : ¹H-n.m.r. data (CDC1₃): δ 4.72 (s. 2 H. methylene), 7.16-8.12 (m, 20 H, 4 phenyl); m/z: 531 (20), 530 (30), 426 (28), 425 (100), 411 (32), 410 (50), 398 (12), 397 (12), 363 (20), 322 (70), 321 (68), 304 (72), 276 (48), 248 (44), 217 (50), 200 (46), 196 (80), 180 (28), 170 (82), 143 (24), 122 (76), 106 (82), 105 (90), 92 (70), 91 (88), 77 (80), 65 (60), and 61 (90).

Anal. Calc. for $C_{31}H_{22}N_4O_5 \cdot 0.5 H_2O$: C, 68.88; H, 4.29; N, 10.36. Found: C, 69.27; H, 4.28; N, 10.56.

Condensation products (13–19) of 3-formyl-4,5(1H)-pyrazolinedione 4-(phenyl-hydrazone). — A solution of aldehyde 8 (0.1 g) in ethanol (20 mL) was treated under reflux with the respective hydroxylamine, arylhydrazine. semicarbazide, and thiosemicarbazide (one molar proportion) and a few drops of acetic acid. Each product crystallized from ethanol in orange crystals (see Table 1). Mass-spectral data for compound 18: m/z 274 (30). 273 (100), 256 (80). 230 (36), 229 (72), 212 (22), 199 (36), 189 (36), 171 (25), 130 (28), 125 (36), 122 (11), 106 (12), 105 (60), 104 (18), 92 (70), 91 (12), 93 (17), 78 (46), and 77 (66).

Pyrazole imidazole derivative (20). — A solution of 8 (0.1 g) in ethanol (20 mL) was treated with *o*-phenylenediamine (0.1 g) in ethanol (20 mL) containing a few drops of acetic acid. The mixture was boiled under reflux, and cooled to room temperature, and the solid was filtered off, washed with ether, and dried (yield 30 mg). Compound 20 crystallized from methanol in orange needles, m.p. 239–240 : $v_{max}^{\rm KB1}$ 1660 cm⁻¹ (OCN).

Anal. Cale. for $C_{16}H_{14}N_6O$: C, 62.74: H, 4.60: N, 27.42. Found: C, 62.40; H, 4.32; N, 27.00.

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